AMENDMENTS

In the Specification

Amended Paragraph Bridging Pages 4 and 5

In random or shotgun DNA sequencing, a large DNA fragment (typically one larger than 20,000 base pairs) is broken into smaller fragments that are inserted into a cloning vector. It is assumed that the sum of information contained within these smaller clones is equivalent to that contained within the original DNA fragment. Numerous smaller clones are randomly selected, DNA templates are prepared for sequencing reactions, and primers that will base-pair with the vector DNA sequence bordering the insert are used to begin the sequencing reaction (2-7 days for a 20 kbp insert). Subsequently, the quality of each base call is examined (manually or automatically via software (PHRED, Ewing et al., 1998); 1-10 minutes per sequence reaction), and the sequence of the original DNA fragment is reconstructed by computer assembly of the sequences obtained from the smaller DNA fragments. Based on the time estimates provided, if a shotgun sequencing strategy is used, a 20 kbp insert is expected to be completed in 3-10 days. This strategy was extensively used to determine the sequence of ordered fragments that represent the entire human genome (see the United States Government website nhgri.nih, the HGP sublink ~~http://www.nhgri.nih.gov/HGP/~~). However, this random approach is typically not sufficient to complete sequence determination, since gaps in the sequence often remain after computer assembly. A directed strategy (described below) is usually used to complete the sequence project.

B1

Amended Paragraph Bridging Pages 5 and 6

One of the original goals of the Human Genome Project was to complete sequence determination of the entire human genome by 2005 (see the United States Government website nhgri.nih, the HGP sublink ~~http://www.nhgri.nih.gov/HGP/~~). However, the plan is ahead of schedule and a 'working draft' of the human genome was published in February 2001 (Venter er al., 2001, "International Human Genome Sequencing Consortium 2001"). Due to technological advances in several disciplines, the completed genome sequence is expected in 2003, two years ahead of schedule. Progress in all aspects involving DNA manipulation (especially manipulation and propagation of large DNA fragments), evolution of faster and better DNA sequencing methods (see the website abrf.org ~~http://www.abrf.org~~), development of computer hardware and software capable of manipulating and analyzing the data (bioinformatics), and automation of procedures associated with generating and analyzing DNA sequences (engineering) are responsible for this accelerated time frame.

B2

If it would be of assistance in resolving any issues in this application, the Examiner is kindly invited to contact applicant's attorney Robert W. Strozier at 713.977.7000

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Respectfully submitted,

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